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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/547,669	09/02/2005	Daniele Calistri	2503-1170	1643

466 7590 03/28/2007

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EXAMINER	
STAPLES, MARK	
ART UNIT	PAPER NUMBER
1637	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/28/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/547,669	CALISTRI ET AL.	
	Examiner	Art Unit	
	Mark Staples	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) *7 and 12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 8-11* is/are rejected.

7)☒ Claim(s) *3, 8, and 10* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 September 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *09/02/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of claims 1-6 and 8-11 of Group I and SEQ ID NOs: 9, 10, 13, 14, 15, and 16 in the reply filed on 01/22/07 is acknowledged. Lack of unity was established between Group I and Group II claims, which Applicant does not traverse. The traversal is on the ground(s) that that no citation of a reference is provided for the election of primer species. This is not found persuasive because a reference is not required to establish a lack of unity (see MPEP §1875.01).

The requirement is still deemed proper and is therefore made FINAL.

Claims 7 and 12 withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected species and an invention respectively, there being no allowable generic or linking claim. SEQ ID NOs: 11 and 12 as recited in claim 6 are also withdrawn as being drawn to non elected species. Applicant timely traversed the restriction (election) requirement in the reply filed on 01/22/07.

In summary, claims 1-6 and 8-11 of Group I and SEQ ID NOs: 9, 10, 13, 14, 15, and 16 as filed on 01/22/07 will be fully examined for patentability.

Information Disclosure Statement

2. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a

separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Specification

3. The use of the trademarks VIC™ and PET™ have been noted in this application. They and any other trademarks should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Objections

4. Claim 3 is objected to because of the following informalities: claim 3 does not end in a period. Appropriate correction is required.

5. Claim 8 is objected to because of the following informalities: claim 8 does not end in a period. Appropriate correction is required.

6. Claim 10 is objected to because of the following informalities: the apparent misspelling "calorimetric"; it appears "colorimetric" is intended. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-6 and 8-11 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: determining the presence of colorectal tumors or precancerous lesions as recited in the preamble of claim 1. While claim 1 recites quantitation, calculation, and comparison of amplified fragments, there is no step relating these steps to determining the presence of colorectal tumors or precancerous lesions.

8. Claims 1-6 and 8-11 are rejected under 35 U.S.C. 112, second paragraph, as failing to recite active steps. While minute details are not required in method claims, at least the basic steps must be recited in a positive, active fashion. See Ex parte Erlich, 3 USPQ2d, p. 1011 (Bd. Pat. App. Int. 1986).

9. Claim 3 contains the trademark/trade names HEX™, 6-FAM™, and TAMRA™. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods

themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe fluorescent molecules and, accordingly, the identification/description is indefinite.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claim 1-6 and 8-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Although recited in claim 1, the specification does not describe how the presence of pre-cancerous lesions can be determined.

12. The following table is given for the discussion of prior art which follows.

Table 1

100% Sequence Matches for SEQ ID NOs: 9, 10, 13, 14, 15, and 16

SEQ ID NO: 9

Search Result 20070214_162645_us-10-547-669a-9.rng.

```
Title:          US-10-547-669A-9
Perfect score:  20
Sequence:       1 aactaccatccagcaacaga 20
RESULT 3

AAF62231/c
```

ID AAF62231 standard; DNA; 37 BP.

AC AAF62231;

DT 21-MAY-2001 (first entry)

DE Probe for human apc2 (adenomatous polyposis coli) gene.

KW Human; detection; cancer; pre-cancer; foetal abnormality; apoptosis;

KW colon cancer; probe; adenomatous polyposis coli; apc; ss.

OS Homo sapiens.

PN WO200118252-A2.

PD 15-MAR-2001.

PF 08-SEP-2000; 2000WO-US024639.

PR 08-SEP-1999; 99US-0152847P.

PR 07-DEC-1999; 99US-00455950.

PA (EXAC-) EXACT LAB INC.

PI Shuber AP;

DR WPI; 2001-235215/24.

PT Detecting a disease (e.g. cancer or pre-cancer), determining its status,

PT or screening a patient for a disease, comprises determining the integrity

PT of nucleic acids in a patient sample containing shed cells or cellular

PT debris.

PS Example 3; Page 20; 44pp; English.

CC A method for determining the disease status of a patient or screening a

CC patient for disease, comprises determining the integrity of nucleic acids

CC in a sample containing cells which have been shed or cellular debris. The

CC method is useful for detecting a disease, determining the disease status

CC of a patient or screening a patient for a disease. The disease may be

CC cancer (e.g. colon cancer, lung cancer, oesophageal cancer, prostate

CC cancer, stomach cancer, pancreatic cancer, liver cancer or lymphoma) or

CC pre-cancer. The methods are also useful for assessing the integrity of

CC DNA in a biological sample or for assessing foetal abnormalities. The

CC methods are also useful as assays for apoptosis. The present sequence
CC represents a probe for human apc2 (adenomatous polyposis coli) DNA, which
CC is used in an example illustrating the use of the method for the
CC detection of colon cancer
SQ Sequence 37 BP; 5 A; 5 C; 12 G; 15 T; 0 U; 0 Other;

Query Match 100.0%; Score 20; DB 4; Length 37;
Best Local Similarity 100.0%; Pred. No. 9.3;
Matches 20; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

```
Qy          1 AACTACCATCCAGCAACAGA 20
              ||||||||||||||||||||
Db         35 AACTACCATCCAGCAACAGA 16
```

SEQ ID NO: 10

Search Result 20070214_162645_us-10-547-669a-10.rng.

Title: US-10-547-669A-10
Perfect score: 20
Sequence: 1 taatttggcataaggcatag 20

RESULT 2
ABA78740
ID ABA78740 standard; DNA; 121 BP.
AC ABA78740;
DT 24-JAN-2002 (first entry)
DE APC mutation correcting oligonucleotide SEQ ID NO: 1586.
KW Human; gene therapy; adenosine deaminase deficiency; p53; beta-globin;
KW retinoblastoma; BRCA1; BRCA2; CFTR; cystic fibrosis; cancer; Factor V;
KW cyclin-dependent kinase inhibitor 2A; CDKN2A; melanoma; APC; HBA1; HBA2;
KW adenomatous polyposis of the colon; Factor VII; Factor IX; thrombosis;
KW haemophilia; alpha thalassaemia; haemoglobin alpha locus 1; MLH1; APOE;

KW mismatch repair; MSH2; MSH6; hyperlipidaemia; apolipoprotein E; LDLR;
KW familial hypercholesterolaemia; UGT1; syndrome; APP; PSEN1; antisense;
KW UDP-glucuronosyltransferase; amyloid precursor protein; presenilin-1;
KW Alzheimer's disease; cytostatic; antisickling; antianaemic; haemostatic;
KW antilipemic; ss.

OS Homo sapiens.

PN WO200173002-A2.

PD 04-OCT-2001.

PF 27-MAR-2001; 2001WO-US009761.

PR 27-MAR-2000; 2000US-0192176P.

PR 27-MAR-2000; 2000US-0192179P.

PR 01-JUN-2000; 2000US-0208538P.

PR 30-OCT-2000; 2000US-0244989P.

PA (UYDE) UNIV DELAWARE.

PI Kmiec EB, Gamper HB, Rice MC;

DR WPI; 2001-639230/73.

XX

PT Oligonucleotide for targeted alterations of genetic sequences and for
PT treating cystic fibrosis, comprises at least one mismatch and chemical
PT modification.

PS Claim 7; Page 139; 294pp; English.

CC The present invention provides single-stranded oligonucleotides which can
CC be used for the targeted alteration of genomic sequences, where the
CC oligonucleotide has at least one mismatch compared with the genomic
CC sequence to be altered. In particular, these sequences are directed at
CC the following genes: adenosine deaminase, p53, beta-globin,
CC retinoblastoma, BRCA1, BRCA2, CFTR, cyclin-dependent kinase inhibitor 2A
CC (CDKN2A), APC, Factor V, Factor VIII, Factor IX, haemoglobin alpha locus

CC 1 (HBA1), haemoglobin alpha locus 2 (HBA2), MLH1, MSH2, MSH6,
CC apolipoprotein E (APOE), LDL receptor (LDLR), UDP-glucuronosyltransferase
CC (UGT1), amyloid precursor protein (APC), presenilin-1 (PSEN1) and
CC presenilin-2 (PSEN2). These can be used in the gene therapy of diseases
CC such as cancer, adenosine deaminase deficiency, cystic fibrosis,
CC haemophilia, hypercholesterolaemia, thalassaemia, sickle cell anaemia,
CC Alzheimer's disease, melanoma, adenomatous polyposis of the colon and
CC various syndromes. The present sequence is one of the gene correcting
CC oligonucleotides of the invention
SQ Sequence 121 BP; 30 A; 20 C; 25 G; 46 T; 0 U; 0 Other;

Query Match 100.0%; Score 20; DB 4; Length 121;
Best Local Similarity 100.0%; Pred. No. 3.1;
Matches 20; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

```
Qy          1 TAATTTGGCATAAGGCATAG 20
              ||||||||||||||||||||
Db          4 TAATTTGGCATAAGGCATAG 23
```

SEQ ID NO: 13

Search Result 20070214_162645_us-10-547-669a-13.rng.

Title: US-10-547-669A-13
Perfect score: 20
Sequence: 1 gatgtaatcagacgacacag 20
RESULT 2
ABA78836/c
ID ABA78836 standard; DNA; 121 BP.
AC ABA78836;

DT 24-JAN-2002 (first entry)

DE APC mutation correcting oligonucleotide SEQ ID NO: 1682.

KW Human; gene therapy; adenosine deaminase deficiency; p53; beta-globin;
KW retinoblastoma; BRCA1; BRCA2; CFTR; cystic fibrosis; cancer; Factor V;
KW cyclin-dependent kinase inhibitor 2A; CDKN2A; melanoma; APC; HBA1; HBA2;
KW adenomatous polyposis of the colon; Factor VII; Factor IX; thrombosis;
KW haemophilia; alpha thalassaemia; haemoglobin alpha locus 1; MLH1; APOE;
KW mismatch repair; MSH2; MSH6; hyperlipidaemia; apolipoprotein E; LDLR;
KW familial hypercholesterolaemia; UGT1; syndrome; APP; PSEN1; antisense;
KW UDP-glucuronosyltransferase; amyloid precursor protein; presenilin-1;
KW Alzheimer's disease; cytostatic; antisickling; antianaemic; haemostatic;
KW antilipemic; ss.

OS Homo sapiens.

PN WO200173002-A2.

PD 04-OCT-2001.

PF 27-MAR-2001; 2001WO-US009761.

PR 27-MAR-2000; 2000US-0192176P.

PR 27-MAR-2000; 2000US-0192179P.

PR 01-JUN-2000; 2000US-0208538P.

PR 30-OCT-2000; 2000US-0244989P.

PA (UYDE) UNIV DELAWARE.

PI Kmiec EB, Gamper HB, Rice MC;

DR WPI; 2001-639230/73.

PT Oligonucleotide for targeted alterations of genetic sequences and for
PT treating cystic fibrosis, comprises at least one mismatch and chemical
PT modification.

PS Claim 7; Page 144; 294pp; English.

CC The present invention provides single-stranded oligonucleotides which can
CC be used for the targeted alteration of genomic sequences, where the
CC oligonucleotide has at least one mismatch compared with the genomic
CC sequence to be altered. In particular, these sequences are directed at
CC the following genes: adenosine deaminase, p53, beta-globin,
CC retinoblastoma, BRCA1, BRCA2, CFTR, cyclin-dependent kinase inhibitor 2A
CC (CDKN2A), APC, Factor V, Factor VIII, Factor IX, haemoglobin alpha locus
CC 1 (HBA1), haemoglobin alpha locus 2 (HBA2), MLH1, MSH2, MSH6,
CC apolipoprotein E (APOE), LDL receptor (LDLR), UDP-glucuronosyltransferase
CC (UGT1), amyloid precursor protein (APC), presenilin-1 (PSEN1) and
CC presenilin-2 (PSEN2). These can be used in the gene therapy of diseases
CC such as cancer, adenosine deaminase deficiency, cystic fibrosis,
CC haemophilia, hypercholesterolaemia, thalassaemia, sickle cell anaemia,
CC Alzheimer's disease, melanoma, adenomatous polyposis of the colon and
CC various syndromes. The present sequence is one of the gene correcting
CC oligonucleotides of the invention
SQ Sequence 121 BP; 30 A; 24 C; 19 G; 48 T; 0 U; 0 Other;

Query Match 100.0%; Score 20; DB 4; Length 121;
Best Local Similarity 100.0%; Pred. No. 1.5;
Matches 20; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

```
Qy          1 GATGTAATCAGACGACACAG 20
              ||||||||||||||||||||
Db         78 GATGTAATCAGACGACACAG 59
```

SEQ ID NO: 14

Search Result 20070214_162645_us-10-547-669a-14.rng

Title: US-10-547-669A-14
Perfect score: 20
Sequence: 1 ggcaatcgaacgactctcaa 20

RESULT 2

ABA78883/c

ID ABA78883 standard; DNA; 121 BP.

AC ABA78883;

DT 24-JAN-2002 (first entry)

DE APC mutation correcting oligonucleotide SEQ ID NO: 1729.

KW Human; gene therapy; adenosine deaminase deficiency; p53; beta-globin;
KW retinoblastoma; BRCA1; BRCA2; CFTR; cystic fibrosis; cancer; Factor V;
KW cyclin-dependent kinase inhibitor 2A; CDKN2A; melanoma; APC; HBA1; HBA2;
KW adenomatous polyposis of the colon; Factor VII; Factor IX; thrombosis;
KW haemophilia; alpha thalassaemia; haemoglobin alpha locus 1; MLH1; APOE;
KW mismatch repair; MSH2; MSH6; hyperlipidaemia; apolipoprotein E; LDLR;
KW familial hypercholesterolaemia; UGT1; syndrome; APP; PSEN1; antisense;
KW UDP-glucuronosyltransferase; amyloid precursor protein; presenilin-1;
KW Alzheimer's disease; cytostatic; antisickling; antianaemic; haemostatic;
KW antilipemic; ss.

OS Homo sapiens.

PN WO200173002-A2.

PD 04-OCT-2001.

PF 27-MAR-2001; 2001WO-US009761.

PR 27-MAR-2000; 2000US-0192176P.

PR 27-MAR-2000; 2000US-0192179P.

PR 01-JUN-2000; 2000US-0208538P.

PR 30-OCT-2000; 2000US-0244989P.

PA (UYDE) UNIV DELAWARE.

PI Kmiec EB, Gamper HB, Rice MC;

DR WPI; 2001-639230/73.

PT Oligonucleotide for targeted alterations of genetic sequences and for
PT treating cystic fibrosis, comprises at least one mismatch and chemical
PT modification.

PS Claim 7; Page 146; 294pp; English.

CC The present invention provides single-stranded oligonucleotides which can
CC be used for the targeted alteration of genomic sequences, where the
CC oligonucleotide has at least one mismatch compared with the genomic
CC sequence to be altered. In particular, these sequences are directed at
CC the following genes: adenosine deaminase, p53, beta-globin,
CC retinoblastoma, BRCA1, BRCA2, CFTR, cyclin-dependent kinase inhibitor 2A
CC (CDKN2A), APC, Factor V, Factor VIII, Factor IX, haemoglobin alpha locu s
CC 1 (HBA1), haemoglobin alpha locus 2 (HBA2), MLH1, MSH2, MSH6,
CC apolipoprotein E (APOE), LDL receptor (LDLR), UDP-glucuronosyltransferase
CC (UGT1), amyloid precursor protein (APC), presenilin-1 (PSEN1) and
CC presenilin-2 (PSEN2). These can be used in the gene therapy of diseases
CC such as cancer, adenosine deaminase deficiency, cystic fibrosis,
CC haemophilia, hypercholesterolaemia, thalassaemia, sickle cell anaemia,
CC Alzheimer's disease, melanoma, adenomatous polyposis of the colon and
CC various syndromes. The present sequence is one of the gene correcting
CC oligonucleotides of the invention

SQ Sequence 121 BP; 28 A; 29 C; 28 G; 36 T; 0 U; 0 Other;

Query Match 100.0%; Score 20; DB 4; Length 121;
Best Local Similarity 100.0%; Pred. No. 2.1;
Matches 20; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

```
Qy          1 GGCAATCGAACGACTCTCAA 20
              ||||||||||||||||||||
Db         92 GGCAATCGAACGACTCTCAA 73
```

SEQ ID NO: 15

Search Result 20070214_162645_us-10-547-669a-15.rng.

Title: US-10-547-669A-15
Perfect score: 20
Sequence: 1 cagtgatcttccagatagcc 20

RESULT 5

AAA93450

ID AAA93450 standard; cDNA; 8229 BP.

AC AAA93450;

DT 16-JAN-2001 (first entry)

DE Human APC (DP2.5) cDNA (splice variant 2).

KW APC gene; Adenomatous Polyposis Coli gene; human; chromosome 5q21;

KW familial adenomatous polyposis; FAP locus; Gardner's syndrome; GS;

KW sporadic tumour; adenoma; carcinoma; cancer; lung; breast; colon; rectum;

KW bladder; liver; sarcoma; stomach; prostate; leukaemia; lymphoma;

KW tumour suppressor; anti-APC antibody; detection; diagnosis; prognosis;

KW genetic predisposition; drug screening; DP2.5; splice variant; ds.

OS Homo sapiens.

PN US6114124-A.

PD 05-SEP-2000.

PF 25-MAY-1995; 95US-00450582.

PR 16-JAN-1991; 91GB-00000962.

PR 16-JAN-1991; 91GB-00000963.

PR 16-JAN-1991; 91GB-00000974.

PR 16-JAN-1991; 91GB-00000975.

PR 08-AUG-1991; 91US-00741940.

PR 12-AUG-1994; 94US-00289548.

PA (ICIL) IMPERIAL CHEM IND PLC.

PA (UYJO) UNIV JOHNS HOPKINS.

PA (UTAH) UNIV UTAH.

PA (CANC-) CANCER INST.

PI Carlson M, Groden J, Joslyn G, Kinzler K, Markham AF, Anand R;

PI Albertsen H, White RL, Thliveris A, Nakamura Y, Vogelstein B;

PI Hedge PJ;

DR WPI; 2000-565003/52.

DR P-PSDB; AAB23012.

PT Detecting Adenomatous Polypopsis Coli (APC) protein in a sample for

PT diagnosing cancers, involves contacting the sample with antibodies that

PT specifically bind to APC protein and detecting the complex formed.

PS Example 7; Fig 7A1-7W; 125pp; English.

CC The invention relates to a novel method for detecting Adenomatous

CC Polyposis Coli (APC) protein in a sample. The method involves contacting

CC the sample with antibodies which specifically binds to the 2843 amino

CC acid form of the human APC protein, or to a mutant APC protein, and

CC detecting an APC-antibody complex. Mutations in the APC gene play a role

CC in tumorigenesis, indicating that it is a tumour suppressor gene. It is

CC located on chromosome 5q21, which corresponds to the FAP (familial

CC adenomatous polyposis) locus. FAP is an autosomal dominant inherited

CC disease in which affected individuals develop hundreds to thousands of

CC adenomatous polyps in the colon and rectum, some of which progress to

CC malignancy. The FAP locus is often found to be deleted in sporadic (i.e.,

CC non-familial) adenomas and carcinomas, and chromosome 5q deletions have

CC also been observed in tumours of the lung, breast, colon, rectum,

CC bladder, liver, sarcomas, stomach, and prostate, and in leukaemias and

CC lymphomas. Although the FAP locus contains several other genes such as

CC FER, TB1, TB2, and MCC, it is thought that mutations in the APC gene play

CC a key role in the development of FAP and sporadic tumours. The method is

CC useful for detecting APC protein and its mutant forms in foetal tissue,
CC placental tissue, amniotic fluid, blood, serum or a tumour sample. The
CC method is useful for diagnosing or prognosing neoplastic tissue, for
CC detecting a genetic predisposition to cancer, for detecting germline and
CC somatic alteration of wild-type APC genes, and for testing therapeutic
CC agents for the ability to suppress tumours. The present sequence
CC represents cDNA encoding a 2742 amino acid splice variant of the human
CC APC protein

SQ Sequence 8229 BP; 2863 A; 1702 C; 1670 G; 1994 T; 0 U; 0 Other;

Query Match 100.0%; Score 20; DB 3; Length 8229;
Best Local Similarity 100.0%; Pred. No. 9.8;
Matches 20; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

Qy 1 CAGTGATCTTCCAGATAGCC 20
||||||||||||||||||||
Db 3957 CAGTGATCTTCCAGATAGCC 3976

SEQ ID NO: 16

Search Result 20070214_162645_us-10-547-669a-16.rng.
Title: US-10-547-669A-16
Perfect score: 20
Sequence: 1 aaatggctcatcgaggctca 20
RESULT 2
ABA78900
ID ABA78900 standard; DNA; 121 BP.
AC ABA78900;

DT 24-JAN-2002 (first entry)

DE APC mutation correcting oligonucleotide SEQ ID NO: 1746.

KW Human; gene therapy; adenosine deaminase deficiency; p53; beta-globin;
KW retinoblastoma; BRCA1; BRCA2; CFTR; cystic fibrosis; cancer; Factor V;
KW cyclin-dependent kinase inhibitor 2A; CDKN2A; melanoma; APC; HBA1; HBA2;
KW adenomatous polyposis of the colon; Factor VII; Factor IX; thrombosis;
KW haemophilia; alpha thalassaemia; haemoglobin alpha locus 1; MLH1; APOE;
KW mismatch repair; MSH2; MSH6; hyperlipidaemia; apolipoprotein E; LDLR;
KW familial hypercholesterolaemia; UGT1; syndrome; APP; PSEN1; antisense;
KW UDP-glucuronosyltransferase; amyloid precursor protein; presenilin-1;
KW Alzheimer's disease; cytostatic; antisickling; antianaemic; haemostatic;
KW antilipemic; ss.

OS Homo sapiens.

PN WO200173002-A2.

PD 04-OCT-2001.

PF 27-MAR-2001; 2001WO-US009761.

PR 27-MAR-2000; 2000US-0192176P.

PR 27-MAR-2000; 2000US-0192179P.

PR 01-JUN-2000; 2000US-0208538P.

PR 30-OCT-2000; 2000US-0244989P.

PA (UYDE) UNIV DELAWARE.

PI Kmiec EB, Gamper HB, Rice MC;

DR WPI; 2001-639230/73.

PT Oligonucleotide for targeted alterations of genetic sequences and for
PT treating cystic fibrosis, comprises at least one mismatch and chemical
PT modification.

PS Claim 7; Page 147; 294pp; English.

CC The present invention provides single-stranded oligonucleotides which can
CC be used for the targeted alteration of genomic sequences, where the
CC oligonucleotide has at least one mismatch compared with the genomic
CC sequence to be altered. In particular, these sequences are directed at
CC the following genes: adenosine deaminase, p53, beta-globin,
CC retinoblastoma, BRCA1, BRCA2, CFTR, cyclin-dependent kinase inhibitor 2A
CC (CDKN2A), APC, Factor V, Factor VIII, Factor IX, haemoglobin alpha locus
CC 1 (HBA1), haemoglobin alpha locus 2 (HBA2), MLH1, MSH2, MSH6,
CC apolipoprotein E (APOE), LDL receptor (LDLR), UDP-glucuronosyltransferase
CC (UGT1), amyloid precursor protein (APC), presenilin-1 (PSEN1) and
CC presenilin-2 (PSEN2). These can be used in the gene therapy of diseases
CC such as cancer, adenosine deaminase deficiency, cystic fibrosis,
CC haemophilia, hypercholesterolaemia, thalassaemia, sickle cell anaemia,
CC Alzheimer's disease, melanoma, adenomatous polyposis of the colon and
CC various syndromes. The present sequence is one of the gene correcting
CC oligonucleotides of the invention

SQ Sequence 121 BP; 38 A; 26 C; 24 G; 33 T; 0 U; 0 Other;

Query Match 100.0%; Score 20; DB 4; Length 121;
Best Local Similarity 100.0%; Pred. No. 1.9;
Matches 20; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

```
Qy          1 AAATGGCTCATCGAGGCTCA 20
              ||||||||||||||||||||
Db         24 AAATGGCTCATCGAGGCTCA 43
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13. In view of the claim rejections given above, the following claim interpretations have been made in order to determine whether prior art is applicable.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 1, 2, 4-6, and 9-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Shuber (WO 2001/42502, published on 14 June 2001 and listed on the Information Disclosure Statement, IDS).

Regarding claims 1, 2, 5 and 9, Shuber teaches a method for determining the presence of colorectal tumors in a human subject (entire reference), which comprises:
a) DNA extraction from stool samples (see p. 18, 1st paragraph: "After homogenization, nucleic acid is preferably isolated from the stool sample. . . .The extracted nucleic acids are then precipitated with alcohol. . . . Total DNA is isolated using techniques known in the art");
b) PCR amplification of at least three different DNA fragments with a length of 100 base pairs or more, using deoxynucleotide triphosphates or primers labelled with detectable markers (see p. 4, 2nd paragraph, 6th sentence: "It is preferable that, in the case of DNA,

the amplification reaction is a polymerase chain reaction (PCR) . . ." ; p. 9, 2nd paragraph : "Methods of the invention also comprise conducting a series of amplification reactions at a series of different genomic loci. . . . Preferably, from about 2 to about 7 amplification reactions on about 2 to about 7 loci are used. . . . In a preferred embodiment, the target fragment lengths are 200 bp, 400 bp, 800 bp, 1.3 Kb, 1.8 Kb, and 2.4 Kb" which are more than 100 base pairs and note that 200 and 400 are between 100 and 500 base pairs as recited in instant claim 5; and p. 8, 2nd paragraph, 3rd sentence: "Labels, such as fluorescent or radioactive labels, may be used" which also applies to instant claim 2);

c) quantitation of the amplified fragments (amplicons);

d) calculation of the total amount of different amplicons;

e) comparison of the values obtained in (d) with a reference value (for steps c, d, and e see Figures 1 through 10, where quantitation is given as "Q#", which is calculated by interpolation, as recited in instant claim 9, from a standard curve consisting of known amounts of DNA, and compared to the "NEG CONTROL" as a reference value, and in Figures 1-7 is also compared to the "POSITIVE CONTROL" as another reference value).

Regarding claims 4 and 6, Shuber teaches a method wherein at least 8 different DNA fragments are amplified (12 loci for amplification are taught which is at least eight, as given on p. 8, 1st paragraph, last sentence: "Preferred disease-associated loci include p53, apc, MSH-2, dcc, scr, c-myc, B-catnenin, mlh-1 , pms-I , pms-2, pol-delta, and bax").

Regarding claim 10, Shuber teaches spectrophotometric detection systems (see p. 8, 2nd paragraph, 3rd sentence: "The amounts of amplification product produced may be compared to standard amounts by any suitable or convenient means, including, but not limited to . . . machine-driven optical comparison, densitometry, . . . and other known means").

Regarding claim 11, Shuber teaches a method where the reference value is determined from healthy (normal) subjects/patients (See p. 3, 2nd paragraph, 5th sentence: "Thus, tumor cells are typically intact and routinely are shed into, for example, stool, sputum, urine, bile, pancreatic juice, and blood. Such shed cells and cellular debris contain higher integrity nucleic acids and other cellular components compared to those found in specimens obtained from a healthy patient"; and see p. 10, 2nd paragraph, 3rd sentence: "A baseline for comparison of the extent of nucleic acid amplification can be amounts of nucleic acids from known normal samples").

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

16. Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Shuber (2001) as applied to claims 1 and 2 above, and further in view of Tian et al. (2001).

Shuber teaches as noted above.

Shuber does not specifically teach 6-carboxy-fluorescein, 6-FMA™.

Regarding claim 3, Tian et al. teach the fluorescent label 6-carboxy-fluorescein, 6-FMA™ (entire reference, see especially p. 175, 2nd column and Figure 1).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Shuber by using the fluorescent label 6-carboxy-fluorescein as suggested by Tian et al. with a reasonable expectation of success. The motivation to do so is provided by Tian et al. who teach that mutations can be detected with primers labeled with the fluorescent dye 6-carboxy-fluorescein for detection of cancer (see Methods section on p. 173). Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

17. Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Shuber (2001) as applied to claims 1 and 6 above, and further in view of either Kmiec et al. by themselves (W0 2001/73002, published 4 October 2001 and listed on the IDS) or in view of Kmiec et al. and Albertsen et al. (US Paten No.: 6,114,124 issued 2001) and in further view of Buck et al. (1999).

Shuber teaches as noted above, including amplification of APC fragments and teaches a sequence comprising SEQ ID NO: 9 (see Table 1 above).

Shuber does not teach other elected sequences of instant claim 8 or sequences comprising these.

Kmiec et al. teach sequences comprising SEQ ID NO: 10 and 16, and teaches sequences comprising the sequences in primer pairs SEQ ID NOs: 13 and 14 (see Table 1 above).

Kmiec et al. do not teach SEQ ID NOs: 9 and 15 or sequences comprising these.

Albertsen et al. teach a sequence comprising SEQ ID NO: 15 (see Table 1 above).

Albertsen et al. do not teach SEQ ID NOs: 9, 10, 13, 14, or 16; or sequences comprising these.

Buck et al. do not teach SEQ ID NOs: 9, 10, 13, 14, 15, or 16; or sequences comprising these.

Claim 8 is rejected for SEQ ID NOs: 9, 10, 13, 14, 15, and 16, as described following. With regard to Claim 8, for primers designed for amplification of APC gene, Shuber, Kmeic et al. and Alberston et al. expressly disclose the identical nucleic acid

sequences presented in SEQ ID NOs: 9, 10, 13, 14, 15, and 16 of the instant invention. It is noted that the instant primer sites of SEQ ID NOs: SEQ ID NO: 9, 10, 13, 14, 15, and 16 are contained within the sequences disclosed by Shuber, Kmeic et al. and Alberston et al.

The above described references do not specifically disclose the identical primer sequences of SEQ ID NO: 9, 10, 13, 14, 15, and 16 of the primers pairs, respectively, used in the claimed invention.

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers of the APC gene and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations.

Buck et al (1999) expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532,

column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

Conclusion

18. No claim is free of the prior art.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Staples whose telephone number is (571) 272-9053. The examiner can normally be reached on Monday through Thursday, 9:00 a.m. to 7:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Mark Staples MS
Examiner
Art Unit 1637
March 21, 2007

KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER
3/21/07